Treatment with $^{90}Y/^{177}Lu$ DOTATOC in patients with metastatic adrenocortical carcinoma expressing somatostatin receptors

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Abstract

Context: We investigated the role of ^{68}Ga-DOTATOC PET/CT in detecting somatostatin receptors (SSTRs) in 19 patients with metastatic adrenocortical carcinoma (ACC) and explored the activity of 90Y/177Lu-DOTATOC Peptide Receptor Radionuclide Therapy (PRRT).

Case description and methods. ^{68}Ga uptake in metastatic sites was scored in terms of intensity and anatomical uptake distribution of standard uptake value (SUV). Tissue expression of SSTR2A and SSTR5 was also evaluated by immunohistochemistry (IHC) on primary tumors. Eight patients (42%) displayed radiometabolic uptake of any grade intensity with focal and limited distribution. Two patients (11%) displayed strong uptake in multiple lesions and were treated with PRRT. Both obtained an overall disease control lasting 4 and 12 months, respectively.

Conclusions. ACC can express SSTRs as detected by IHC and ^{68}Ga-DOTATOC PET. SSTRs-based PRRT may represent a potential treatment opportunity for a minority of advanced ACC patients. This treatment modality deserves further investigation.

Précis

More than 50% of advanced ACC patients displays detectable levels of somatostatin receptors by means of ^{68}Ga DOTATOC-PET/CT, but only a minority of them are eligible to Peptide Receptor Radionuclide Therapy.

Introduction

Patients with metastatic adrenocortical carcinoma (ACC) generally display poor prognosis (1,2) and limited therapeutic options are available when disease is progressing after first line chemotherapy and mitotane (3).

Somatostatin (SMS) in endocrine cells has both regulatory functions on endocrine and esocrine secretory activities and anti-proliferative properties. SMS analogues represent a standard therapy in the management of neuroendocrine tumors (NET) (4). Currently available SMS analogues (SSAs), octreotide and lanreotide, bind to 2 of the 5 classes of SMS receptors (SSTRs), described in neuroendocrine cells (SSTRs 2 and 5). These SSAs are the radiolabeled peptides for PET imaging and Peptide Receptor Radionuclide Therapy (PRRT) (5).

Few studies investigated SSTRs expression in ACC and none explored the therapeutic role of SSTRs in ACC patients (6-8).

In this study, we evaluated SSTRs expression and reported the results of ^{90}Y/^{177}Lu -DOTATOC PRRT in advanced ACC patients.

Methods

^{68}Ga-DOTATOC-PET/CT was performed in 19 patients with metastatic ACC from two reference centers for ACC in Italy. Patients had been previously treated with surgery, mitotane and chemotherapy. Fifteen patients underwent ^{18}F-FDG-PET/CT (FDG-PET) that was positive in all of them.

Uptake of ^{68}Ga-DOTATOC in metastatic sites was scored in terms of standard uptake value (SUV) intensity (weak/strong, being “strong” similar or superior to liver uptake) and anatomical uptake distribution (focal/multiple-diffuse). Tissue expression of SSTRs 2A and 5 was also evaluated by

immunohistochemistry (IHC) on specimens from primary tumors in 14/19 (74%) patients. Detailed IHC methods and scoring system have been published elsewhere (9).

Results and case description

Baseline characteristics of the 19 patients are given in Table 1. SSTR2A and SSTR5 immunoreactivity with 3+ scores were detected in 2/14 (14%) of patients (Figure 1D-E). Tissue expression of SSTR2A correlated with ^{68}Ga-DOTATOC imaging patterns by a Fisher's test (p=0.011). ^{68}Ga-DOTATOC uptake of any grade intensity was observed in metastatic lesions of ten ACC patients (53%). However, only two patients displayed a clinically significant and strong uptake with a diffuse/multiple pattern. Both patients were offered the ^{90}Y- and ^{177}Lu-DOTATOC PRRT, according to the DOTATER1_26_15 prospective study approved by the Ethical Committee at the Reggio Emilia Hospital in Italy (EudraCT: 2015-005546-63) and signed an informed consent.

Case 1. In 2002, a 30 yr-old female patient underwent left adrenalectomy and lung metastasectomy for a non-secretory, low-grade (Ki-67 10%) ACC. Surgery was radical (R0) and the patient started adjuvant mitotane. After 5 years, the disease relapsed in lungs and mediastinal lymphnodes. Because of oligometastatic, slowly proliferating disease, mitotane was continued until November 2011 and then discontinued after 4 years of tretament. In June 2013, a CT revealed one large (> 5 cm) liver metastasis and a left paravertebral lesion. The patient refused polychemotherapy and was treated with percutaneous radiofrequency ablation. In November 2014, new lung and mediastinal metastases were detected. A ^{68}Ga-DOTATOC-PET/CT revealed diffuse and strong uptake at multiple metastatic lesions in lung, thoracic wall, mediastinal nodes and T11 vertebral body (Figure 1A). In March 2015, the patient was enrolled in the DOTATER1_26_15 study and received 4 cycles of PRRT obtaining a partial response, in terms of either tumor shrinkage and metabolic down-staging, which lasted 12 months (Figure 1B). In March

2018, the disease further progressed. The patient refused other treatments and died of progressing ACC in April 2019.

Case 2. In November 2005, a 25 yr-old male patient underwent surgical resection of a ACC. Surgery was complicated by tumor rupture and peritoneal dissemination of tumor cells. In January 2006, he underwent salvage surgery for local relapse and entered the follow-up program. In November 2012, he experienced a further abdominal recurrence that was surgically resected. Histology confirmed low-grade ACC (Ki67 10%). In January 2013, he started post-operative mitotane therapy. In May 2014, a CT scan revealed multiple small lung metastases, three subcentimetric liver metastases, and a large osteolytic lesion in the left iliac bone. Total body FDG-PET/CT did not show any uptake except for the osteolytic bone lesion. He started first line chemotherapy with cisplatin and etposide plus palliative radiotherapy on the osteolytic lesion (30 Gy). After 8 chemotherapy cycles, a partial response was observed and the patient was maintained on mitotane. On September 2015, the disease progressed again in the lungs and liver. A second-line chemotherapy with gemcitabine and capecitabine was introduced but disease progression occurred 9 months later and a vast osteolytic lesion involving the left iliac wing and sacrum was observed. Because of severe, opioid-unresponsive pain, the bone lesion underwent re-irradiation. In December 2017, ^{68}Ga-DOTATOC-PET/CT was performed showing a strong ^{68}Ga uptake in the large osteolytic bone lesion (Figure 1C). Other small metastatic lesions in the lung, liver and lymph nodes did not show significant uptake. From January to February 2017, the patient was treated with PRRT leading to a disease stabilization that lasted 4 months and was associated with improvement of bone pain and reduced opioid need. The main side effects were mild back pain and WHO G2 lymphopenia. The treatment was interrupted after 2 cycles due to the occurrence of a large bone fracture, which forced the patient to bed. He initiated a third line chemotherapy with temozolomide, but died in July 2017 for disease progression.

Conclusions

Available data on IHC analysis of SSTRs 1-5 expression in ACC showed that SSTRs have an overall low expression with low intensity. Unger et al. found heterogeneous patterns of distribution of SSTRs 1-5 with less than 30% of staining intensity (6). Similar results were obtained by Germano et al., who reported variable expression in 29% (SSTR2) and 84% (SSTR4) of 58 ACC patients. However, treatment of the H295R cell line with the multi-ligand SSA pasireotide, alone or in combination with mitotane and/or everolimus, did not have any significant impact on cell growth (7). Mariniello et al. demonstrated overexpression of SSTRs 1 and 2 in 13/13 samples of ACC patients. Again, they found that pasireotide had antisecretory but not antiproliferative effect on the H295R cell line (8).

In this prospective case series, we demonstrated the presence of SSTR2A and SSTR5 receptors by means of ^{68}Ga-DOTATOC PET/CT in more than 50% of patients with advanced ACC. However, median SUV level was overall weak and the pattern of ^{68}Ga distribution among neoplastic lesions was often focal and heterogeneous. Intratumoral heterogeneity accounted for irregular distribution of SSTR 2 and 5 within tumor lesions while maintaining FDG uptake. In only 2 patients (11%), the uptake of ^{68}Ga was strong enough to make them eligible to PRRT, which led to overall disease control that was long-lasting in one case.

Parallel IHC analysis of SSTR2A and SSTR5 on primary tumor tissue demonstrated IHC expression in 43% and 57% of patients, respectively. Of note, SSTR2A tissue expression was scored 3+ in the two patients with strong and diffuse uptake in ^{68}Ga-DOTATOC PET/CT, and a correlation between tissue immunoreactivity and radiometabolic ^{68}Ga uptake was shown, thus confirming previous observations (10).

According to the teranostic principles, ^{68}Ga-DOTA-peptide PET/CT is an imaging modality able to select a minority of advanced ACC that could benefit from PRRT. Interestingly, both patients with significant ^{68}Ga uptake had low-grade ACC. In light of the paucity of effective treatments for advanced ACC, we believe that ^{90}Y/^{177}Lu-DOTATOC PRRT may deserve further investigation. Given to its safety profile, PRRT is feasible in heavily pretreated patients and may be tested particularly in this setting.

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Figure 1. SSTR expression by ^{68}Ga-DOTATOC PET imaging and immunohistochemistry.

A - Patient #9 baseline imaging of lung and pleural metastases.

B - Patient #9 after 4 treatments with PRRT.

C – Patient #7 baseline imaging of bone metastasis by ^{68}Ga uptake. White arrows and squares indicate metastatic lesions. IHC analysis of (D) SSTR2A and (E) SSTR5 showing strong immunoreactivity (score 3+) in more than 10% of cells (patient #9 [case 1]).

Table 1. Baseline characteristics of patients.

Legend of Table 1. Pt: patient; ENSAT: European Network for the Study of Adrenal Tumors; SUV: standard uptake value; FDG-PET: ^{18}Fluoro-D-glucose positron emission tomography; PRRT: Peptide Receptor Radionuclide Therapy; age, stage and Ki67 are at diagnosis; NP: not performed; NA: not available.

Pt, sex	Age	ENSAT stage	Ki67%	SSTR-2A	SSTR-5	Hormone secretion	Metastatic pattern	N. of previous treatments	^{68}Ga-Dotatoc uptake/ SUV intensity & pattern	FDG-PET uptake	PRRT/ # cycles
1/F	49	2	50	2+	0	Cortisol, aldosterone	Lung, liver, abdomen	3	Yes/strong/focal	Yes	No
2/M	55	3	30	NP	NP	None	Lung	1	Yes/weak/focal	Yes	No
3/F	37	3	>20	1+	1+	None	Lung, liver, nodes, abdomen, bone	4	Yes/weak/focal	Yes	No
4/F	57	2	25	0	0	Cortisol	Lung, nodes	1	No/-/absent	Yes	No
5/F	39	2	40	2+	1+	None	Lung, liver, abdomen, bone	5	Yes/weak/multiple	Yes	No
6/F	61	3	20	0	1+	None	Lung, liver, nodes, abdomen	2	No/-/absent	Yes	No
7/M	25	2	10	3+	2+	None	Lung, liver, nodes, bone	2	Yes/strong/diffuse	Yes	Yes/2
8/M	63	2	30	1+	0	None	Lung, liver, nodes	3	No/-/absent	Yes	No
9/F	55	3	10	3+	3+	None	Lung, nodes, bone	1	Yes/strong/multiple	NA	Yes/4
10/F	66	1	8	0	0	None	Liver, abdomen	3	No/-/absent	Yes	No
11/F	44	2	>20	NP	NP	None	Lung, abdomen	5	Yes/weak/focal	Yes	No
12/M	35	3	5	0	0	Aldosterone	Lung, liver	1	Yes/weak/focal	NA	No
13/F	58	3	10	0	1+	Cortisol	Lung, liver, nodes, abdomen	3	No/-/absent	Yes	No
14/F	49	3	>20	NP	NP	None	Lung, liver	3	No/-/absent	NA	No
15/F	52	2	>20	0	2+	None	Local, liver, ovary	3	No/-/absent	Yes	No
16/F	26	4	>20	0	3+	Cortisol	Lung, liver, nodes, abdomen	0	Yes/weak/focal	Yes	No
17/F	50	4	5	NP	NP	Cortisol	Lung, bone	1	Yes/strong/focal	Yes	No
18/F	57	3	10	NP	NP	Cortisol, testosterone	Lung, liver	1	No/-/absent	Yes	No
19/M	64	3	15	0	0	Aldosterone	Lung, liver, peritoneum	2	No/-/absent	Yes	No

Figure 1